PCT/EP2004/003985

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The Patent Office
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1. Your reference

MG/HG/PB60199P

2. Patent application number
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10 APR 2003

11APR03 E799486-1 001030
P01/7700 0.00-0308333.4

0308333.4

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0NN, Great Britain

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

4735870003

Novel Compounds

5. Name of your agent *(if you have one)*

Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)*

7960982003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

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Patents Form 1/77

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Continuation sheets of this form	
Description	23
Claim(s)	2
Abstract	
Drawings	

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Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature M Gibson Date 10-Apr-03

12. Name and daytime telephone number of person to contact in the United Kingdom: M Gibson 01279 644841

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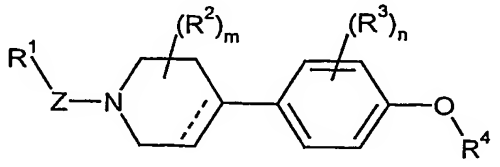
NOVEL COMPOUNDS

The present invention relates to novel phenyl piperidinyl derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurological and psychiatric disorders.

DE 4407139 (Dr Karl Thomae GmbH) describe a series of aminoalkyl-phenyl-azacycloalkanes which are claimed to be useful in the treatment of hyperlipidaemia, atherosclerosis, skin disorders, mycoses and in poultry feed for cholesterol-lean egg production.

The histamine H3 receptor is predominantly expressed in the mammalian central nervous system (CNS), with minimal expression in peripheral tissues except on some sympathetic nerves (Leurs *et al.*, (1998), Trends Pharmacol. Sci. **19**, 177-183). Activation of H3 receptors by selective agonists or histamine results in the inhibition of neurotransmitter release from a variety of different nerve populations, including histaminergic and cholinergic neurons (Schlicker *et al.*, (1994), Fundam. Clin. Pharmacol. **8**, 128-137). Additionally, *in vitro* and *in vivo* studies have shown that H3 antagonists can facilitate neurotransmitter release in brain areas such as the cerebral cortex and hippocampus, relevant to cognition (Onodera *et al.*, (1998), In: The Histamine H3 receptor, ed Leurs and Timmerman, pp255-267, Elsevier Science B.V.). Moreover, a number of reports in the literature have demonstrated the cognitive enhancing properties of H3 antagonists (e.g. thioperamide, clobenpropit, ciproxifan and GT-2331) in rodent models including the five choice task, object recognition, elevated plus maze, acquisition of novel task and passive avoidance (Giovanni *et al.*, (1999), Behav. Brain Res. **104**, 147-155). These data suggest that novel H3 antagonists such as the current series could be useful for the treatment of cognitive impairments in diseases such as Alzheimer's disease and related neurodegenerative disorders.

The present invention provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:

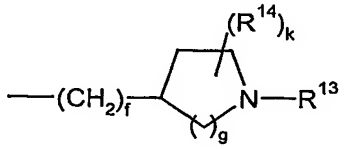


(I)

wherein:

R^1 represents -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heterocyclyl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -aryl-X-aryl, -aryl-X-heteroaryl, -aryl-X-heterocyclyl,- heteroaryl-X-aryl, -heteroaryl-X-heteroaryl, -heteroaryl-X-

heterocyclyl, -heterocyclyl-X-aryl, -heterocyclyl-X-heteroaryl or -heterocyclyl-X-heterocyclyl,
wherein said C_{1-6} alkyl groups of R^1 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{3-7} cycloalkylC_{1-6} alkoxy or C_{1-6} alkanoyl; and
wherein said C_{3-8} cycloalkyl, aryl, heteroaryl and heterocyclyl groups of R^1 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, aryloxy, arylsulfonamido, arylcarboxamido, aroyl, or a group $NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-NR^{15}SO_2R^{16}$ or $-SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl or together form a heterocyclic ring;
X represents a bond, O, CO, OCH_2, CH_2O or SO_2;
Z represents CO, $CONR^{10}$ or SO_2;
R^{10} represents hydrogen, C_{1-6} alkyl, $-C_{3-8}$ cycloalkyl, aryl, heterocyclyl, heteroaryl;
$\overline{\text{----}}$ represents a single or a double bond;
m and n independently represent 0, 1 or 2;
R^2 represents hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy;
R^3 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino, $-COC_{1-6}$ alkyl, $-SO_2C_{1-6}$ alkyl or trifluoromethyl;
R^4 represents $-(CH_2)_q-NR^{11}R^{12}$ or a group of formula (i):



(i)

wherein q is 2, 3 or 4;
$-NR^{11}R^{12}$ represents a heterocyclic group optionally substituted by one or more R^{17} groups;
R^{13} represents hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, $-C_{1-6}$ alkyl-C_{1-6} alkoxy, $-C_{1-6}$ alkyl-C_{3-8} cycloalkyl;
R^{14} and R^{17} independently represent halogen, C_{1-6} alkyl, haloalkyl, OH or C_{1-6} alkoxy;
f is 0 or 1;
g is 1 or 2
k is 0, 1 or 2
or a pharmaceutically acceptable salt thereof.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine and the term 'polyhalo' is used herein to refer to a moiety containing more than one (eg. 2-5) of said halogen atoms.

The term "aryl" includes single and fused rings wherein at least one ring is aromatic, for example, phenyl, naphthyl and tetrahydronaphthalenyl.

The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring or a 4-7 membered saturated or partially unsaturated aliphatic ring fused to a benzene ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur. Suitable examples of such monocyclic rings include pyrrolidinyl, azetidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, diazepanyl and azepanyl. Suitable examples of benzofused heterocyclic rings include indolinyl, isoindolinyl, 2,3,4,5-tetrahydro-1*H*-3-benzazepine or tetrahydroisoquinolinyl.

The term "heteroaryl" is intended to mean a 5-6 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

Preferably, R^1 represents:

-aryl (eg. phenyl) optionally substituted by one or more (e.g. 1 or 2) halogen (eg. 4-fluorine), cyano or SO_2Me groups;

-aryl-X-heterocyclyl (eg. –phenyl-CO-pyrrolidin-1-yl);

-heteroaryl (eg. pyridin-3-yl or pyridin-4-yl);

-heterocyclyl (eg. tetrahydropyranyl, morpholinyl, piperidin-1-yl, pyrrolidin-1-yl, azetidin-1-yl or thiomorpholinyl) optionally substituted by one or more (e.g. 1 or 2) oxo groups; or

-C_{1-6} alkyl-O-C_{1-6} alkyl (eg. $-(CH_2)_2OCH_3$).

More preferably, R^1 represents -heterocyclyl (eg. tetrahydropyranyl) or aryl (eg. phenyl) optionally substituted by a cyano group (eg. 4-cyanophenyl).

Preferably, X represents CO.

Preferably, Z represents CO.

Preferably, ---- represents a single bond.
Preferably, m and n both represent 0.
When R^4 represents $-(CH_2)_q-NR^{11}R^{12}$, preferably q represents 3 or 4 and $-NR^{11}R^{12}$ represents a heterocyclic group (eg. piperidinyl).
When R^4 represents $-(CH_2)_q-NR^{11}R^{12}$, more preferably q represents 3 and $-NR^{11}R^{12}$ represents a heterocyclic group (eg. piperidinyl).
When R^4 represents a group of formula (i), preferably f and k both represent 0, g represents 2 and R^{13} represents C_{1-6} alkyl (eg. i-propyl) or C_{3-8} cycloalkyl (eg. cyclobutyl).
Preferably, R^4 represents $-(CH_2)_q-NR^{11}R^{12}$.

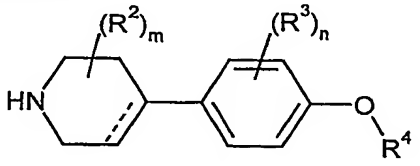
Preferred compounds according to the invention include examples E1-E38 as shown below, or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) preparing a compound of formula (I) wherein Z represents CO which comprises reacting a compound of formula (II)



(II)

or an optionally activated or protected derivative thereof, wherein ----, R^2, R^3, R^4, m and n are as defined above, with a compound of formula R^1-CO-L^1, wherein R^1 is as defined above and L^1 represents a suitable leaving group, such as a hydroxyl group or a suitable halogen atom; or

(b) preparing a compound of formula (I) wherein Z represents SO_2 which comprises reacting a compound of formula (II) as defined above, with a compound of formula R^1-SO_2-L^2, wherein R^1 is as defined above and L^2 represents a suitable leaving group, such as a suitable halogen atom (eg. chlorine); or

(c) preparing a compound of formula (I) wherein Z represents $CONR^{10}$ which comprises reacting a compound of formula (II) as defined above, with a compound of formula R^1-N=C=O, wherein R^1 is as defined above; or

(d) preparing a compound of formula (I) wherein Z represents $CONR^{10}$ which comprises reacting a compound of formula (II) as defined above, with a compound of formula $R^1R^{10}N$-L^3, wherein R^1 and R^{10} are as defined above and L^3 represents hydrogen or a suitable leaving group, such as COCl; or

(e) deprotecting a compound of formula (I) or converting groups which are protected; and optionally thereafter

(f) interconversion to other compounds of formula (I).

When L^1 represents a halogen atom, process (a) typically comprises the use of a suitable base, such as triethylamine in an appropriate solvent such as dichloromethane. When L^1 represents a hydroxyl group, process (a) typically comprises the use of a coupling reagent, such as 1,3-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole in an appropriate solvent such as dichloromethane.

Process (b) typically comprises the use of a base, such as triethylamine in an appropriate solvent such as dichloromethane.

Process (c) is typically conducted in a solvent such as dichloromethane.

When L^3 represents hydrogen, process (d) typically comprises reacting the compound of formula (II) sequentially with phosgene in a suitable solvent such as toluene followed by the compound of formula $R^1R^{10}N$-H in a suitable solvent such as dichloromethane.

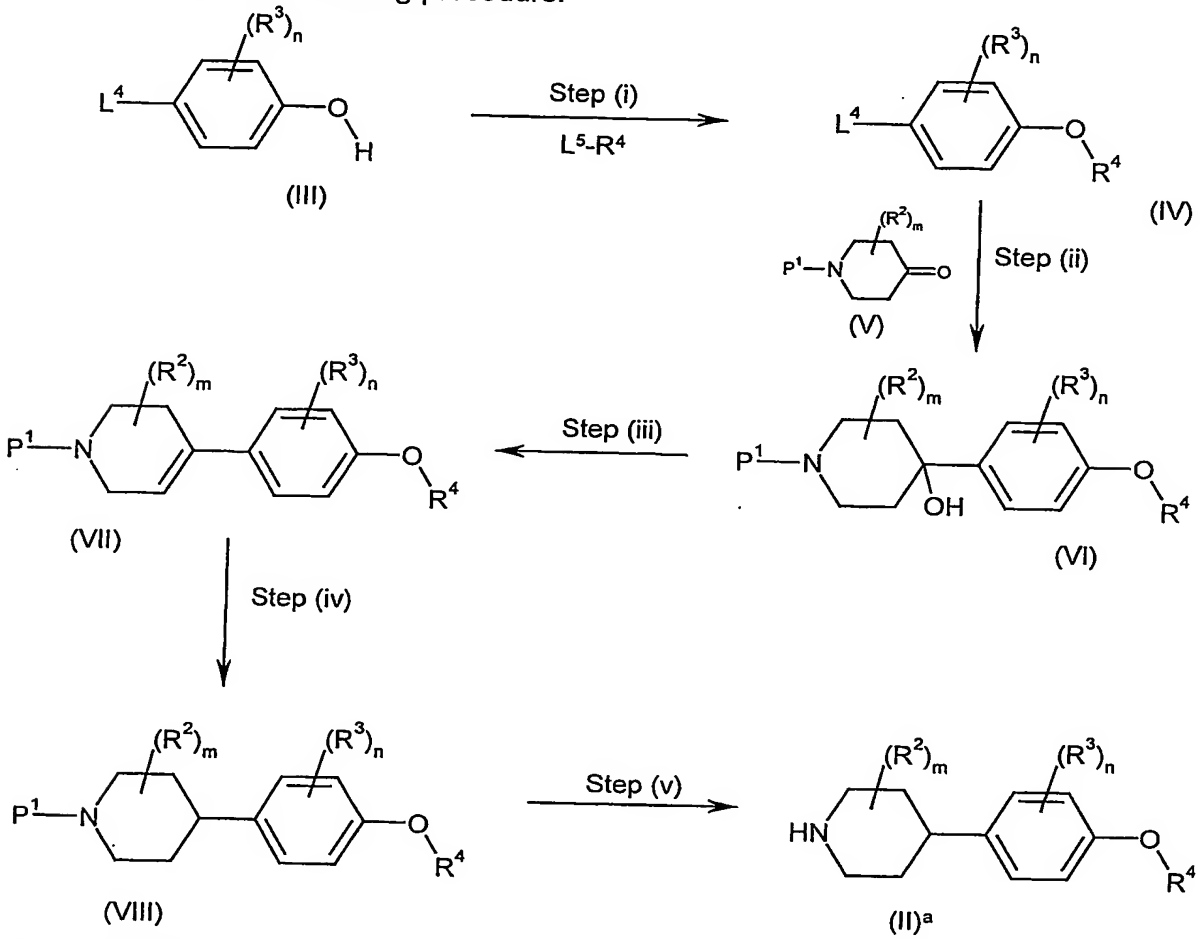
When L^3 represents COCl, process (d) typically comprises the use of a base, such as triethylamine in an appropriate solvent such as dichloromethane.

In process (e), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl

group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (f) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation. For example, compounds of formula (I) wherein R^3 represents a group of formula (i) may be interconverted at the R^{13} position when R^{13} is hydrogen by reductive amination, for example, with acetone in the presence of a borohydride such as sodium triacetoxyborohydride and optionally an acid such as acetic acid in a suitable solvent such as dichloromethane.

Compounds of formula (II) wherein ---- represents a single bond may be prepared in accordance with the following procedure:



wherein R^2, R^3, R^4, m and n are as defined above, L^4 represents a suitable leaving group, such as a halogen atom (eg. iodine), L^5 represents a suitable leaving group, such as a hydroxyl group or a suitable halogen atom; and P^1 represents hydrogen or a suitable protecting group, such as t-butoxycarbonyl.

When L^5 represents a halogen atom (eg. bromine or chlorine), step (i) may be performed using a suitable base, such as potassium carbonate in an appropriate solvent, such as 2-butanone, optionally in the presence of a transfer reagent, such as potassium iodide, at an appropriate temperature such as reflux.

When L^5 represents an optionally activated hydroxyl group, step (i) may be performed using a phosphine such as triphenylphosphine in a suitable solvent such as tetrahydrofuran, followed by addition of an azadicarboxylate such as diethylazaodicarboxylate at a suitable temperature such as room temperature.

Step (ii) may be performed by treating a compound of formula (IV) with an organo metallic reagent such as butyllithium under conditions suitable for metal-halogen exchange followed by treatment with a compound of formula (V).

Step (iii) may be performed under acidic conditions, for example, using trifluoroacetic acid in dichloromethane. Alternatively, steps (iii) and step (iv) may be performed together using a silane, such as triethylsilane, in the presence of an acid, for example, trifluoroacetic acid.

Step (iv) may be performed under transition metal catalysed hydrogenation conditions, for example, under a 50 psi pressure of hydrogen employing a suitable catalyst, such as palladium on charcoal, in a suitable solvent, such as ethanol.

Step (v) may be performed in accordance with the procedures outlined in process (e).

Compounds of formula (II) wherein $\overline{\text{----}}$ represents a double bond may be prepared in an identical manner to the procedure described above with the omission of step (iv).

Compounds of formula (III) and (V) are either known or may be prepared in accordance with known procedures.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for the histamine H3 receptor and are believed to be of potential use in the treatment of neurological diseases including Alzheimer's disease, dementia, age-related memory dysfunction, mild cognitive impairment, cognitive deficit, epilepsy, neuropathic pain, inflammatory pain, Parkinson's disease, multiple sclerosis, stroke and sleep disorders including narcolepsy; psychiatric disorders including schizophrenia (particularly cognitive deficit of schizophrenia), attention deficit hypereactivity disorder, depression and addiction; and other diseases including obesity, asthma, allergic rhinitis, nasal congestion, chronic obstructive pulmonary disease and gastro-intestinal disorders.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or

prophylaxis of the above disorders, in particular neurodegenerative disorders including Alzheimer's disease.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

When used in therapy, the compounds of formula (I) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention further provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Compounds of formula (I) may be used in combination with other therapeutic agents, for example histamine H1 antagonists or medicaments claimed to be useful as either disease modifying or symptomatic treatments of Alzheimer's disease. Suitable examples of such other therapeutic agents may be agents known to modify cholinergic transmission such as 5-HT_6 antagonists, muscarinic agonists or acetylcholinesterase inhibitors. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such

combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

1-Benzyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperidin-4-ol (D1)

A solution of 1-[3-(4-iodophenoxy)-propyl]-piperidine (WO 02/12214) (1.0g, 2.9mmol) in THF (5ml) at –70°C was treated with *n*-butyl lithium (1.6M in hexanes, 2ml, 3.2mmol). After stirring at –70°C for 30 minutes 1-benzyl-piperidine-4-one (548mg, 2.9mmol) was added dropwise and the mixture stirred for 1 hour. Saturated ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield a residue which was purified using silica gel chromatography eluting with a mixture of 0.880 ammonia:ethanol:dichloromethane (0.5:4.5:95) to afford the title compound (550mg, 47%); MS (ES+), m/e 409 $[M+H]^+$.

Description 2

1-Benzyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-1,2,3,6-tetrahydro-pyridine (D2)

To a solution of 1-benzyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperidin-4-ol (D1) (450mg, 1.1mmol) in dichloromethane (5ml) was added trifluoroacetic acid (0.68ml, 8.8mmol) and powdered 4A molecular sieves. After stirring at room temperature for 2 hours the suspension was filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in dichloromethane and stirred with aqueous sodium hydroxide solution for 10 minutes. The organic phase was separated, washed with water and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to afford the title compound (365mg, 85%); MS (ES+), m/e 391 $[M+H]^+$..

Description 3

4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-piperidine (D3)

A solution of 1-benzyl-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-1,2,3,6-tetrahydro-pyridine (D2) (450mg, 1.15mmol) in methanol (40ml) containing palladium on charcoal (10% paste, 200mg) was hydrogenated at 50 p.s.i. at room temperature for 18 hours. The mixture was filtered through filter aid and the filtrate evaporated *in vacuo* to afford the title compound (330mg, 95%); MS (ES+), m/e 303 $[M+H]^+$.

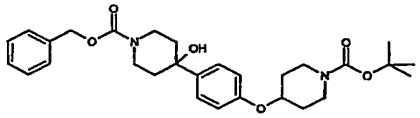
Description 4

4-(4-Iodo-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (D4)

Di-*tert*-butyl azodicarboxylate (57g; 250mmol) was added portionwise to a stirring mixture of 4-iodophenol (50g; 230mmol), triphenyl phosphine (65.6g; 250mmol) and 4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (50g; 250mmol) in dry tetrahydrofuran and cooled to 0°C. The resulting mixture was stirred at room temperature for 3 days. The solvent was removed by filtration and the residue purified by column chromatography on silica eluting with a mixture of n- hexane and ethyl acetate (9:1). Fractions containing the product were combined and evaporated to afford the title compound as a white crystalline solid (63.4g, 63%), MS (ES+), m/e 404 $[M+H]^+$.

Description 5

4-Hydroxy-4-[4-(tert-butoxycarbonyl-piperidin-4-yloxy)-phenyl]-piperidine-1-carboxylic acid benzyl ester (D5)



A solution of 4-(4-iodo-phenoxy)-piperidine-1-carboxylic acid *tert*-butyl ester (10g; 24.8 mM) (D4) in THF (100 ml) at –70°C was treated with *n*-butyl lithium (1.6M in hexanes, 23 ml, 36.8 mmol). After stirring at –70°C for 30 minutes a solution of 4-oxo-piperidine-1-carboxylic acid benzyl ester (8.7 g, 36.8 mmol) in THF was added dropwise and the mixture stirred for 18 hours. Saturated ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield a residue which was purified using silica gel chromatography eluting with a mixture of hexane and ethyl acetate (1:1) to afford the title compound (7.38 g, 56%); MS (ES+), m/e 511 $[M+H]^+$.

Description 6

4-[4-(Piperidin-4-yloxy)-phenyl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester (D6)

Trifluoroacetic acid (12 ml) was added to a stirring solution of 4-hydroxy-4-[4-(tert-butoxycarbonyl-piperidin-4-yloxy)-phenyl]-piperidine-1-carboxylic acid benzyl ester (7.38g; 14.5mmol) (D5) in dichloromethane (12ml) and the mixture stirred for 60 minutes. The solvent was removed by evaporation and the residue filtered through a SCX column eluting with methanol followed by 10% 0.880 ammonia solution in methanol to elute the product (4.9g; 87%), MS (ES+), m/e 393 $[M+H]^+$.

Description 7

4-[4-(1-Isopropyl-piperidin-4-yloxy)-phenyl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester (D7)

Sodium triacetoxyborohydride (5.3g; 25.2mmol) was added portion-wise to a stirring mixture of 4-[4-(piperidin-4-yloxy)-phenyl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester (4.94g; 12.6mmol) (D6) , acetone (5ml; 63mmol) and glacial acetic acid (1ml) in dichloromethane (60ml). The mixture was stirred at room temperature for 18 hours. The mixture was stirred with aqueous sodium hydroxide solution for 10 minutes. The organic phase was separated, washed with water and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to afford the title compound (5.11g, 93%); MS (ES+), m/e 435 $[M+H]^+$.

Description 8

4-[4-(1- Isopropyl-piperidin-4-yloxy)-phenyl]-piperidine (D8)

A solution of 4-[4-(1-isopropyl-piperidin-4-yloxy)-phenyl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester (5.11g, 11.8mmol) (D7) in ethanol (75ml) containing palladium on charcoal (10% paste, 1g) was hydrogenated at 50 p.s.i. at room temperature for 18 hours. The mixture was filtered through filter aid and the filtrate evaporated *in vacuo* to afford the title compound (3.51g, 98%); MS (ES+), m/e 303 $[M+H]^+$.

Description 9

4-[4-(1-Cyclobutyl-piperidin-4-yloxy)-phenyl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester (D9)

Sodium triacetoxyborohydride (2.13g; 10.05mmol) was added portion-wise to a stirring mixture of 4-[4-(piperidin-4-yloxy)-phenyl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester (1.97g; 5.03mmol) (D6), cyclobutanone (0.8ml; 10.05mmol) and 4Å molecular sieves in dichloromethane (50ml). The mixture was stirred at room temperature for 4 hours. The mixture was stirred with aqueous sodium hydroxide solution for 10 minutes. The organic phase was separated, washed with water and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to afford the title compound (1.95g, 87%); MS (ES+), m/e 447 $[M+H]^+$.

Description 10

4-[4-(1- Cyclobutyl-piperidin-4-yloxy)-phenyl]-piperidine (D10)

A solution of 4-[4-(1-cyclobutyl-piperidin-4-yloxy)-phenyl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester (1.95g, 4.37mmol) (D9) in ethanol (40ml) containing palladium on charcoal (10% paste, 400g) was hydrogenated at 50 p.s.i. at room temperature for 18 hours. The mixture was filtered through filter aid and the filtrate evaporated *in vacuo* to afford the title compound (1.34g, 96%); MS (ES+), m/e 315 $[M+H]^+$.

Description 11

4-Hydroxy-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperidine-1-carboxylic acid *tert*-butyl ester (D11)

A solution of 1-[3-(4-iodo-phenoxy)-propyl]-piperidine (WO 02/12214) (10g; 29 mmol) in THF (50 ml) at –70°C was treated with *n*-butyl lithium (1.6M in hexanes, 21.8ml, 34.8mmol). After stirring at –70°C for 30 minutes a solution of 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (6.36g, 31.9mmol) in THF (15 ml) was added dropwise and the mixture stirred for 2 hours. Saturated ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield a residue which was purified using silica gel chromatography eluting with a mixture of 1-9-90 0.88 aqueous ammonia solution-methanol-DCM to afford the title compound (5.2 g, 45%); MS (ES+), m/e 419 $[M+H]^+$.

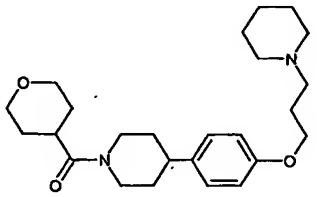
Description 12

4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-1,2,3,6-tetrahydro-pyridine (D12)

Trifluoroacetic acid (6ml) was added to a stirring solution 4-hydroxy-4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperidine-1-carboxylic acid *tert*-butyl ester (3.9g; 9.3mmol) (D11) in dichloromethane (6ml) and the mixture stirred for 60 minutes. The solvent was removed by evaporation and the residue filtered through a SCX column eluting with methanol followed by 10% 0.880 ammonia solution in methanol to elute the product (2.1g; 77%), MS (ES+), m/e 301 $[M+H]^+$.

Example 1

1-{4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-piperidin-1-yl}-1-(tetrahydro-pyran-4-yl)-methanone (E1)



A mixture tetrahydro-pyran-4-carboxylic acid (130mg, 1mmol), 1-hydroxybenzotriazole hydrate (135mg, 1mmol) and N-cyclohexylcarbodiimide-N'-methyl polystyrene (550mg, 1mmol, resin loading 1.8mmol/g) in dichloromethane (8ml) was stirred at room temperature for 15 minutes. A solution of 4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperidine (D3) (151mg, 0.5mmol) in dichloromethane (5ml) was added and the mixture stirred at room temperature for 24 hours. The mixture was filtered through a SCX column eluting with methanol followed by 10% 0.880 ammonia solution in methanol to elute the product. The residue was purified by silica gel chromatography eluting with a 1:9:90 mixture of 0.880 ammonia solution:methanol:dichloromethane to afford the title compound (127mg, 63%); MS(AP+) m/e 415 $[M+H]^+$.

Examples 2-7

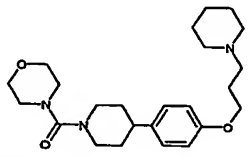
Examples 2-7 (E2-E7) were prepared from 4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperidine (D3) using an analogous method to that described in Example 1 (E1) by

substituting tetrahydro-pyran-4-carboxylic acid for the appropriate acid indicated in the table.

Example	Acid	Mass Spectrum
4-(1-{4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-piperidin-1-yl}-methanoyl)-benzonitrile (E2)	4-cyanobenzoic acid	MS (ES+), m/e 432 $[M+H]^+$.
1-{4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-piperidin-1-yl}-1-pyridin-4-yl-methanone (E3)	Isonicotinic acid	MS (ES+), m/e 408 $[M+H]^+$.
1-{4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-piperidin-1-yl}-1-[4-(1-pyrrolidin-1-yl-methanoyl)-phenyl-methanone (E4)	4-(1-pyrrolidin-1-yl-methanoyl)-benzoic acid	MS (ES+), m/e 504 $[M+H]^+$.
1-(4-Methanesulfonyl-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperidin-1-yl}-methanone (E5)	4-methanesulfonyl-benzoic acid	MS (ES+), m/e 485 $[M+H]^+$.
1-(4-Fluoro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperidin-1-yl}-methanone (E6)	4-fluorobenzoic acid	MS (ES+), m/e 425 $[M+H]^+$.
1-{4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-piperidin-1-yl}-1-pyridin-3-yl-methanone (E7)	Nicotinic acid	MS (ES+), m/e 408 $[M+H]^+$.

Example 8

1-Morpholin-4-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperidin-1-yl}-methanone (E8)



Morpholine-carbonyl chloride (71µl; 0.48mmol) was added to a mixture of 4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperidine (D3) (120mg; 0.4mmol) and diethyaminomethyl-polystyrene (300mg of 3.2 mmol/g) in DCM (5ml). After stirring for 60 minutes the mixture was filtered and the filtrate purified by silica gel chromatography eluting with 1:9:90 mixture of 0.880 ammonia solution:methanol:dichloromethane to afford the title compound (118mg; 62%) MS (ES+), m/e 416 $[M+H]^+$.

Examples 9-10

Examples 9-10 (E9-10) were prepared using the method described for Example 8 substituting morpholine-carbonyl chloride for the appropriate carbonyl chloride indicated in the table.

Example	Carbonyl chloride	Mass Spectrum
1-Piperidin-1-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-piperidin-1-yl}-methanone (E9)	Piperidine-1-carbonyl chloride	MS (ES+), m/e 414 $[M+H]^+$.
1-{4-[4-(3-Piperidin-yl-propoxy)-phenyl]-piperidin-1-yl}-1-pyrrolidin-1-yl-methanone (E10)	Pyrrolidine-1-carbonyl chloride	MS (ES+), m/e 400 $[M+H]^+$.

Example 11

1-(4-Fluoro-phenyl)-1-{4-[4-(1- isopropyl-piperidin-4-yloxy)-phenyl]-piperidin-1-yl}-methanone (E11)

A mixture 4-fluorobenzoic acid (112mg, 0.8mmol), 1-hydroxybenzotriazole hydrate (108mg, 0.8mmol) and N-cyclohexylcarbodiimide-N'-methyl polystyrene (330mg, 0.8mmol, resin loading 1.8mmol/g) in dichloromethane (5ml) was stirred at room temperature for 15 minutes. A solution of 4-[4-(1- isopropyl-piperidin-4-yloxy)-phenyl]-piperidine (120mg, 0.4mmol) (D8) in dichloromethane (3ml) was added and the mixture stirred at room temperature for 24 hours. The mixture was filtered through a SCX column eluting with methanol followed by 10% 0.880 ammonia solution in methanol to elute the product. The residue was purified by silica gel chromatography eluting with a mixture of 0.880 ammonia solution:methanol:dichloromethane (1:9:90) to afford the title compound (78mg, 74%); MS(ES+) m/e 425 $[M+H]^+$.

Examples 12-18

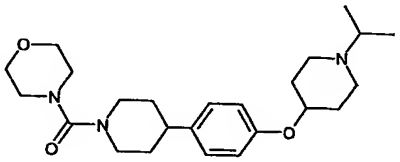
Examples 12-18 (E12-18) were prepared from 4-[4-(1- isopropyl-piperidin-4-yloxy)-phenyl]-piperidine (D8) using an analogous method to that described for Example 11, exchanging 4-fluorobenzoic acid for the appropriate acid indicated in the table below:

Example	Acid	Mass Spectrum
4-(1-{4-[4-(1- Isopropyl-piperidin-4-yloxy)-phenyl]-piperidin-1-yl}-methanoyl)-benzonitrile (E12)	4-cyano-benzoic acid	MS (ES+), m/e 432 $[M+H]^+$.
1-{4-[4-(1-Isopropyl-piperidin-4-yloxy)-phenyl]-piperidin-1-yl}-1-[4-(1-pyrrolidin-1-yl-methanoyl)-phenyl]-methanone (E13)	4-(1-pyrrolidin-1-yl-methanoyl)-benzoic acid	MS (ES+), m/e 504 $[M+H]^+$.
1-{4-[4-(1-Isopropyl-piperidin-4-yloxy)-	Tetrahydro-pyran-4-	MS (ES+), m/e

phenyl-piperidin-1-yl}-1-(tetrahydro-pyran-4-yl)-methanone (E14)	carboxylic acid	415 $[M+H]^+$.
1-{4-[4-(1-Isopropyl-piperidin-4-yloxy)-phenyl-piperidin-1-yl}-1-(4-methanesulfonyl-phenyl)-methanone (E15)	4-methanesulfonyl-benzoic acid	MS (ES+), m/e 485 $[M+H]^+$.
1-{4-[4-(1-Isopropyl-piperidin-4-yloxy)-phenyl-piperidin-1-yl}-3-methoxy-propan-1-one (E16)	3-methoxy-propionic acid	MS (ES+), m/e 415 $[M+H]^+$.
1-{4-[4-(1-Isopropyl-piperidin-4-yloxy)-phenyl-piperidin-1-yl}-1-pyridin-4-yl-methanone (E17)	isonicotinic acid	MS (ES+), m/e 415 $[M+H]^+$.
1-{4-[4-(1-Isopropyl-piperidin-4-yloxy)-phenyl-piperidin-1-yl}-1-pyridin-3-yl-methanone (E18)	nicotinic acid	MS (ES+), m/e 415 $[M+H]^+$.

Example 19

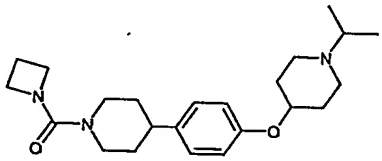
1-{4-[4-(1-Isopropyl-piperidin-4-yloxy)-phenyl]-piperidin-1-yl}-1-morpholin-4-yl-methanone (E19)



Morpholine-carbonyl chloride (71µl; 0.48mmol) was added to a mixture of 4-[4-(1-isopropyl-piperidin-4-yloxy)-phenyl]-piperidine (120mg; 0.4mmol) (D8) and diethyaminomethyl-polystyrene (300mg of 3.2 mmol/g) in DCM (5ml). After stirring for 60 minutes the mixture was filtered and the filtrate purified by silica gel chromatography eluting with 1:9:90 mixture of 0.880 ammonia solution:methanol:dichloromethane to afford the title compound (127mg; 78%) MS (ES+), m/e 416 $[M+H]^+$.

Example 20

1-Azetidin-1-yl-{4-[4-(1- isopropyl-piperidin-4-yloxy)-phenyl]-piperidin-1-yl}-methanone (E20)



A solution of 4-[4-(1- isopropyl-piperidin-4-yloxy)-phenyl]-piperidine (150mg; 0.5mmol) (D8) in DCM (3ml) was added drop-wise to a stirring solution of phosgene in toluene (2ml of 2M soln; 4mmol). After 30 minutes the solvent was removed *in vacuo* and the residue redissolved in DCM (5ml). This solution was treated with triethylamine (146µl;

1.1mmol) and azetidine (37µl; 0.55mmol) and stirred for 60 minutes at room temperature. The mixture was concentrated *in vacuo* and the residue purified by silica gel chromatography eluting with a mixture of 0.880 ammonia solution:methanol:dichloromethane (1:9:90) to afford the title compound (109mg; 58%) MS (ES+), m/e 386 $[M+H]^+$.

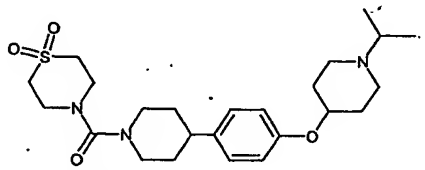
Examples 21-22

Examples 21-22 were prepared from 4-[4-(1- isopropyl-piperidin-4-yloxy)-phenyl]-piperidine (D8) using an analogous method to that described for Example 20, exchanging azetidine for the appropriate amine indicated in the table below:

Example	Amine	Mass Spectrum
1-{4-[4-(1-Isopropyl-piperidin-4-yloxy)-phenyl]-piperidin-1-yl}-1-pyrrolidin-1-yl-methanone (E21)	Pyrrolidine	MS (ES+), m/e 432 $[M+H]^+$.
1-{4-[4-(1-Isopropyl-piperidin-4-yloxy)-phenyl]-piperidin-1-yl}-1-piperidin-1-yl-methanone (E22)	Piperidine	MS (ES+), m/e 504 $[M+H]^+$.

Example 23

1-(1,1-Dioxo-1λ^6-thiomorpholin-4-yl)-1-{4-[4-(1- isopropyl-piperidin-4-yloxy)-phenyl]-piperidin-1-yl}- methanone (E23)



A solution of 4-[4-(1- isopropyl-piperidin-4-yloxy)-phenyl]-piperidine (150mg; 0.5mmol) (D8) in DCM (3ml) was added drop-wise to a stirring solution of phosgene in toluene (2ml of 2M soln; 4mmol). After 30 minutes the solvent was removed *in vacuo* and the residue redissolved in DCM (5ml). This solution was treated with triethylamine (146µl; 1.1mmol) and thiomorpholine 1,1-dioxide (J. Med. Chem. 37(7), 913 - 923, 1994) (148mg; 0.55mmol) and stirred for 60 minutes at room temperature. Methylisocyanate polystyrene (1.1g of 1.8 mmol/g resin; 2mmol) was added and the mixture stirred at room temperature for 30 minutes. The mixture was filtered and the filtrate was purified by silica gel chromatography eluting with a mixture of 0.880 ammonia solution:methanol:dichloromethane (1:9:90) to afford the title compound (122mg, 53%); MS(ES+) m/e 464 $[M+H]^+$.

Examples 24-29

Examples 24-29 (E24-E29) were prepared from 4-[4-(1-cyclobutyl-piperidin-4-yloxy)-phenyl]-piperidine (D10) using an analogous method to that described for Example 11 (E11), using the appropriate acid indicated in the table below:

Example	Acid	Mass Spectrum
4-(1-{4-[4-(1- Cyclobutyl-piperidin-4-yloxy)-phenyl]-piperidin-1-yl}-methanoyl)-benzonitrile (E24)	4-cyano-benzoic acid	MS (ES+), m/e 444 $[M+H]^+$.
1-(4-Fluoro-phenyl)-1-{4-[4-(1-cyclobutyl-piperidin-4-yloxy)-phenyl]-piperidin-1-yl}- methanone (E25)	4-fluorobenzoic acid	MS(ES+) m/e 437 $[M+H]^+$.
1-{4-[4-(1-Cyclobutyl-piperidin-4-yloxy)-phenyl]-piperidin-1-yl}-1-[4-(1-pyrrolidin-1-yl-methanoyl)-phenyl]-methanone (E26)	4-(1-pyrrolidin-1-yl-methanoyl)-benzoic acid	MS (ES+), m/e 516 $[M+H]^+$.
1-{4-[4-(1-Cyclobutyl -piperidin-4-yloxy)-phenyl-piperidin-1-yl}-3-methoxy-propan-1-one (E27)	3-methoxy-propionic acid	MS (ES+), m/e 401 $[M+H]^+$.
1-{4-[4-(1-Cyclobutyl -piperidin-4-yloxy)-phenyl-piperidin-1-yl}-1-pyridin-4-yl-methanone (E28)	isonicotinic acid	MS (ES+), m/e 420 $[M+H]^+$.
1-{4-[4-(1-Cyclobutyl-piperidin-4-yloxy)-phenyl-piperidin-1-yl}-1-pyridin-3-yl-methanone (E29)	nicotinic acid	MS (ES+), m/e 420 $[M+H]^+$.

Example 30

1-{4-[4-(1-Cyclobutyl -piperidin-4-yloxy)-phenyl]-piperidin-1-yl}-1-morpholin-4-yl-methanone (E30)

Morpholine-carbonyl chloride (60µl; 0.52mmol) was added to a mixture of 4-[4-(1-cyclobutyl-piperidin-4-yloxy)-phenyl]-piperidine (148mg; 0.47mmol) (D10) and triethylamine (80µl; 0.56mmol) in DCM (5ml). After stirring for 18 hours mixture was filtered through a SCX column eluting with methanol followed by 10% 0.880 ammonia solution in methanol to elute the product. The product was purified further by silica gel chromatography eluting with a 1:9:90 mixture of 0.880 ammonia solution:methanol:dichloromethane to afford the title compound (175mg, 92%); MS(ES+) m/e 427 $[M+H]^+$.

Example 31

1-(4-Fluoro-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-methanone (E31)

A mixture 4-fluorobenzoic acid (140mg, 1.0mmol), 1-hydroxybenzotriazole hydrate (135mg, 1.0mmol) and N-cyclohexylcarbodiimide-N'-methyl polystyrene (550mg, 1.0mmol, resin loading 1.8mmol/g) in dichloromethane (5ml) was stirred at room temperature for 15 minutes. A solution of 4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-1,2,3,6-tetrahydro-pyridine (150mg, 0.5mmol) (D12) in dichloromethane (3ml) was added and the mixture stirred at room temperature for 24 hours. The mixture was filtered through a SCX column eluting with methanol followed by 10% 0.880 ammonia solution in methanol to elute the product. The residue was purified by silica gel chromatography eluting with a 1:9:90 mixture of 0.880 ammonia solution:methanol:dichloromethane to afford the title compound (137mg, 64%); MS(ES+) m/e 423 $[M+H]^+$.
(137mg, 64%); MS(ES+) m/e 423 $[M+H]^+$.

Examples 32-35

Examples 32-35 (E32-E35) were prepared from 4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-1,2,3,6-tetrahydro-pyridine (D12) using an analogous method to that described for Example 31 using the appropriate acid indicated in the table below

Example	Acid	Mass Spectrum
4-(1-{4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-methanoyl)-benzonitrile (E32)	4-cyano-benzoic acid	MS (ES+), m/e 430 $[M+H]^+$.
1-{4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-1-[4-(1-pyrrolidin-1-yl-methanoyl)-phenyl]-methanone (E33)	4-(1-pyrrolidin-1-yl-methanoyl)-benzoic acid	MS (ES+), m/e 502 $[M+H]^+$.
1-{4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-1-(tetrahydro-pyran-4-yl)-methanone (E34)	tetrahydropyran-4-carboxylic acid	MS (ES+), m/e 413 $[M+H]^+$.
1-(4-Methanesulfonyl-phenyl)-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-methanone (E35)	4-methanesulfonyl benzoic acid	MS (ES+), m/e 483 $[M+H]^+$.

Example 36

1-Morpholin-4-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-methanone (E36)

Morpholine-carbonyl chloride (116µl; 0.55mmol) was added to a mixture of 4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-1,2,3,6-tetrahydro-pyridine (150mg; 0.5mmol) (D12) and diethyaminomethyl-polystyrene (330mg of 3.2 mmol/g) in DCM (5ml). After stirring for 60 minutes the mixture was filtered and the filtrate purified by silica gel chromatography

eluting with 1:9:90 mixture of 0.880 ammonia solution:methanol:dichloromethane to afford the title compound (126mg; 62%) MS (ES+), m/e 414 $[M+H]^+$.

Examples 37-38

Examples 37-38 (E37-E38) were prepared from 4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-1,2,3,6-tetrahydro-pyridine (D12) using an analogous method to that described for Example 36, using the appropriate carbonyl chloride indicated in the table below:

Name	Carbonyl Chloride	Mass Spectrum
1-Piperidin-1-yl-1-{4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-methanone (E37)	Piperidine carbonyl chloride	(ES+), m/e 412 $[M+H]^+$.
1-{4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-3,6-dihydro-2*H*-pyridin-1-yl}-1-pyrrolidin-1-yl-methanone (E38)	Pyrrolidine carbonyl chloride	(ES+), m/e 398 $[M+H]^+$.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Biological Data

A membrane preparation containing histamine H3 receptors may be prepared in accordance with the following procedures:

(i) Generation of histamine H3 cell line

DNA encoding the human histamine H3 gene was cloned into a holding vector, pCDNA3.1 TOPO (InVitrogen) and its cDNA was isolated from this vector by restriction digestion of plasmid DNA with the enzymes BamH1 and Not-1 and ligated into the inducible expression vector pGene (InVitrogen) digested with the same enzymes. The GeneSwitch™ system (a system where in transgene expression is switched off in the absence of an inducer and switched on in the presence of an inducer) was performed as described in US Patent nos: 5,364,791; 5,874,534; and 5,935,934. Ligated DNA was transformed into competent DH5α *E. coli* host bacterial cells and plated onto Luria Broth (LB) agar containing Zeocin™ (an antibiotic which allows the selection of cells expressing the *sh ble* gene which is present on pGene and pSwitch) at 50μg ml^{-1}. Colonies containing the re-ligated plasmid were identified by restriction analysis. DNA for transfection into mammalian cells was prepared from 250ml cultures of the host bacterium containing the pGeneH3 plasmid and isolated using a DNA preparation kit (Qiagen Midi-Prep) as per manufacturers guidelines (Qiagen).

CHO K1 cells previously transfected with the pSwitch regulatory plasmid (InVitrogen) were seeded at 2x10e6 cells per T75 flask in Complete Medium, containing Hams F12

(GIBCOBRL, Life Technologies) medium supplemented with 10% v/v dialysed foetal bovine serum, L-glutamine, and hygromycin (100μg ml^{-1}), 24 hours prior to use. Plasmid DNA was transfected into the cells using Lipofectamine plus according to the manufacturers guidelines (InVitrogen). 48 hours post transfection cells were placed into complete medium supplemented with 500μg ml^{-1} Zeocin™.

10-14 days post selection 10nM Mifepristone (InVitrogen), was added to the culture medium to induce the expression of the receptor. 18 hours post induction cells were detached from the flask using ethylenediamine tetra-acetic acid (EDTA; 1:5000; InVitrogen), following several washes with phosphate buffered saline pH 7.4 and resuspended in Sorting Medium containing Minimum Essential Medium (MEM), without phenol red, and supplemented with Earles salts and 3% Foetal Clone II (Hyclone). Approximately 1x 10e7 cells were examined for receptor expression by staining with a rabbit polyclonal antibody, 4a, raised against the N-terminal domain of the histamine H3 receptor, incubated on ice for 60 minutes, followed by two washes in sorting medium. Receptor bound antibody was detected by incubation of the cells for 60 minutes on ice with a goat anti rabbit antibody, conjugated with Alexa 488 fluorescence marker (Molecular Probes). Following two further washes with Sorting Medium, cells were filtered through a 50μm Filcon™ (BD Biosciences) and then analysed on a FACS Vantage SE Flow Cytometer fitted with an Automatic Cell Deposition Unit. Control cells were non-induced cells treated in a similar manner. Positively stained cells were sorted as single cells into 96-well plates, containing Complete Medium containing 500μg ml^{-1} Zeocin™ and allowed to expand before reanalysis for receptor expression via antibody and ligand binding studies. One clone, 3H3, was selected for membrane preparation.

(ii) Membrane preparation from cultured cells

All steps of the protocol are carried out at 4°C and with pre-cooled reagents. The cell pellet is resuspended in 10 volumes of buffer A2 containing 50mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (pH 7.40) supplemented with 10e-4M leupeptin (acetyl-leucyl-leucyl-arginal; Sigma L2884), 25μg/ml bacitracin (Sigma B0125), 1mM ethylenediamine tetra-acetic acid (EDTA), 1mM phenylmethylsulfonyl fluoride (PMSF) and 2x10e-6M pepstain A (Sigma). The cells are then homogenised by 2 x 15 second bursts in a 1 litre glass Waring blender, followed by centrifugation at 500g for 20 minutes. The supernatant is then spun at 48,000g for 30 minutes. The pellet is resuspended in 4 volumes of buffer A2 by vortexing for 5 seconds, followed by homogenisation in a Dounce homogeniser (10-15 strokes). At this point the preparation is aliquoted into polypropylene tubes and stored at -70°C.

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following assays:

(I) Histamine H3 binding assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10µl of test compound (or 10µl of iodophenpropit (a known histamine H3 antagonist) at a final concentration of 10mM) diluted to the required concentration in 10% DMSO;

(b) 10µl ^{125}I 4-[3-(4-iodophenylmethoxy)propyl]-1H-imidazolium (iodoproxyfan) (Amersham; 1.85MBq/µl or 50µCi/ml; Specific Activity ~2000Ci/mmol) diluted to 200pM in assay buffer (50mM Tris(hydroxymethyl)aminomethane buffer (TRIS) pH 7.4, 0.5mM ethylenediamine tetra-acetic acid (EDTA)) to give 20pM final concentration; and

(c) 80µl bead/membrane mix prepared by suspending Scintillation Proximity Assay (SPA) bead type WGA-PVT at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 80µl which contains 7.5µg protein and 0.25mg bead per well – mixture was pre-mixed at room temperature for 60 minutes on a roller.

The plate is shaken for 5 minutes and then allowed to stand at room temperature for 3-4 hours prior to reading in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data was analysed using a 4-parameter logistic equation.

(II) Histamine H3 functional antagonist assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10µl of test compound (or 10µl of guanosine 5'- triphosphate (GTP) (Sigma) as non-specific binding control) diluted to required concentration in assay buffer (20mM N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) + 100mM NaCl + 10mM $MgCl_2$, pH7.4 NaOH);

(b) 60µl bead/membrane/GDP mix prepared by suspending wheat germ agglutinin-polyvinyltoluene (WGA-PVT) scintillation proximity assay (SPA) beads at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 60µl which contains 10µg protein and 0.5mg bead per well – mixture is pre-mixed at 4°C for 30 minutes on a roller and just prior to addition to the plate, 10µM final concentration of guanosine 5' diphosphate (GDP) (Sigma; diluted in assay buffer) is added;

The plate is incubated at room temperature to equilibrate antagonist with receptor/beads by shaking for 30 minutes followed by addition of:

(c) 10µl histamine (Tocris) at a final concentration of 0.3µM; and

(d) 20µl guanosine 5' [γ35-S] thiotriphosphate, triethylamine salt (Amersham; radioactivity concentration = 37kBq/µl or 1mCi/ml; Specific Activity 1160Ci/mmol) diluted to 1.9nM in assay buffer to give 0.38nM final.

The plate is then incubated on a shaker at room temperature for 30 minutes followed by centrifugation for 5 minutes at 1500 rpm. The plate is read between 3 and 6 hours after completion of centrifuge run in a Wallac Microbeta counter on a 1 minute normalised

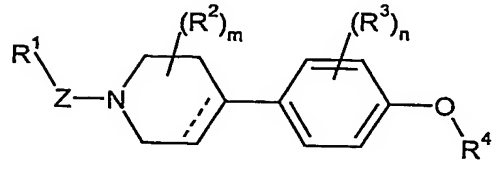
tritium count protocol. Data is analysed using a 4-parameter logistic equation. Basal activity used as minimum i.e. histamine not added to well.

Results

The compounds of Examples E1-E38 were tested in the histamine H3 functional antagonist assay and exhibited pK_b values > 8.5.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 represents -C_{1-6} alkyl-O-C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heterocyclyl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -aryl-X-aryl, -aryl-X-heteroaryl, -aryl-X-heterocyclyl,- heteroaryl-X-aryl, -heteroaryl-X-heteroaryl, -heteroaryl-X-heterocyclyl, -heterocyclyl-X-aryl, -heterocyclyl-X-heteroaryl or -heterocyclyl-X-heterocyclyl,

wherein said C_{1-6} alkyl groups of R^1 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{3-7} cycloalkylC_{1-6} alkoxy or C_{1-6} alkanoyl; and

wherein said C_{3-8} cycloalkyl, aryl, heteroaryl and heterocyclyl groups of R^1 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, aryloxy, arylsulfonamido, arylcarboxamido, aroyl, or a group $NR^{15}R^{16}$, -$CONR^{15}R^{16}$, -$NR^{15}COR^{16}$, -$NR^{15}SO_2R^{16}$ or -$SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl or together form a heterocyclic ring;

X represents a bond, O, CO, OCH_2, CH_2O or SO_2;

Z represents CO, $CONR^{10}$ or SO_2;

R^{10} represents hydrogen, C_{1-6} alkyl, -C_{3-8} cycloalkyl, aryl, heterocyclyl, heteroaryl;

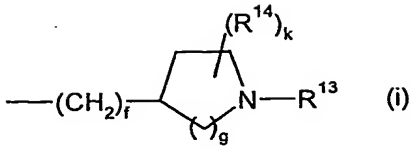
---- represents a single or a double bond;

m and n independently represent 0, 1 or 2;

R^2 represents hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy;

R^3 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino, -COC_{1-6} alkyl, -SO_2C_{1-6} alkyl or trifluoromethyl;

R^4 represents -$(CH_2)_q$-$NR^{11}R^{12}$ or a group of formula (i):



(i)

wherein q is 2, 3 or 4;
$-NR^{11}R^{12}$ represents a heterocyclic group optionally substituted by one or more R^{17} groups;
R^{13} represents hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, $-C_{1-6}$ alkyl-C_{1-6} alkoxy, $-C_{1-6}$ alkyl-C_{3-8} cycloalkyl;
R^{14} and R^{17} independently represent halogen, C_{1-6} alkyl, haloalkyl, OH or C_{1-6} alkoxy;
f is 0 or 1;
g is 1 or 2
k is 0, 1 or 2
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 which is a compound of formula E1-E38 or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or claim 2 for use in therapy.

4. A compound according to claim 1 or claim 2 for use in the treatment of Alzheimer's disease.

5. A pharmaceutical composition which comprises a compound according to claim 1 or claim 2 and a pharmaceutically acceptable carrier or excipient.